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(19) (CA) **CANADIAN PATENT** (12)

(54) Process for the Preparation of 7-[2-(2-Aminothiazol-4-YL)-2-Hydroxyiminoacetamido]-3-Cephem Compounds

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(30) (GB) U.K. 8800295 1988/01/07

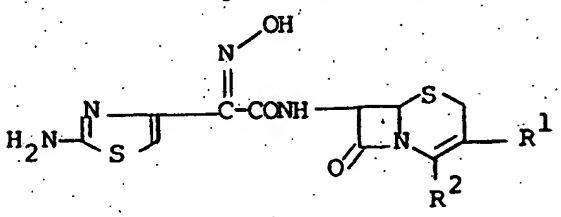
(57) 3 Claims

NO DRAWING

527,693-1

ABSTRACT

There are described 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem or salts thereof of the general formula:



wherein R^1 is an organic group and
R^2 is carboxy or protected hydroxy.

These compounds are prepared in high yield from the corresponding 7-amino-3-cephem compounds and 2-(2-aminothiazol-4-yl)-2-acyloxyiminoacetyl halide or a salt thereof. These compounds exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic micro-organisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents. Intermediates useful for the preparation of these compounds are also described.

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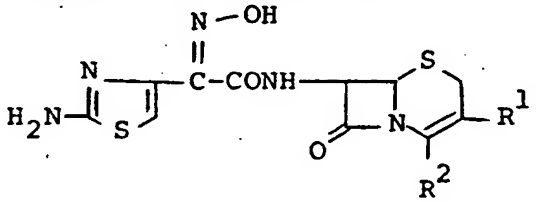
PROCESS FOR THE PREPARATION OF 7-[2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-3-CEPHEM COMPOUNDS

The present invention relates to a novel process for the preparation of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds or a salt thereof.

More particularly, it relates to a novel process for the preparation of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds, which can be represented by the following general formula, or a salt thereof from the corresponding 7-amino-3-cephem compounds and 2-(2-aminothiazol-4-yl)-2-acyloxyiminoacetyl halide or a salt thereof in high yield.



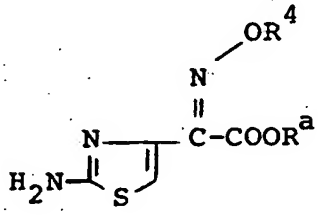
(I)

wherein R^1 is an organic group and
R^2 is carboxy or protected carboxy.

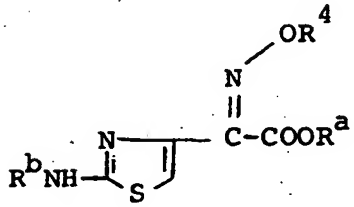
Accordingly, the object of the present invention is to provide a new industrial process for the preparation of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds (I) or a salt thereof.

In the past, 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds (I) are prepared, for example, by the following methods.

Method 1 :



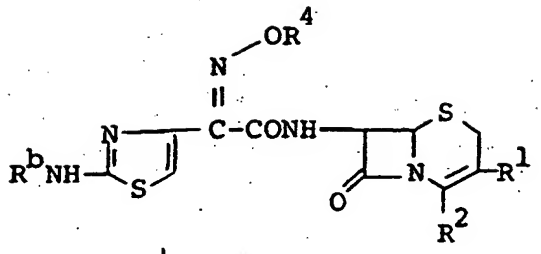
Introduction of amino-protective group



(1) Elimination of carboxy-protective group

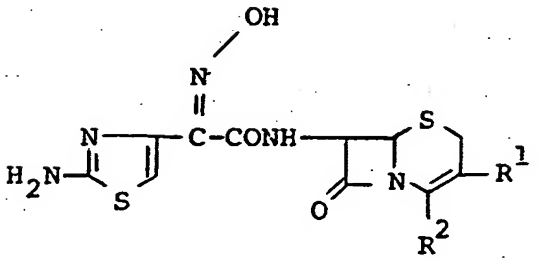
(2) Conversion of its reactive derivative at the carboxy group

(3) Reaction with 7-amino-3-cephem compounds



(1) Elimination of amino-protective group

(2) Elimination of the hydroxy-protecting group

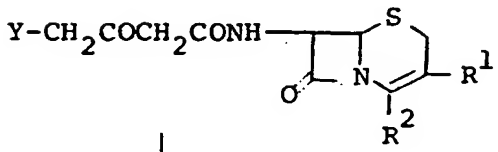


(I)

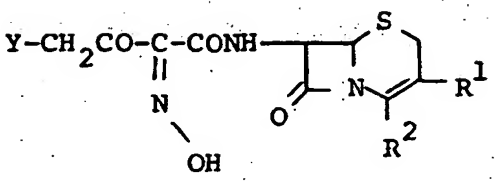
Method 2 :

$Y\text{-}CH_2COCH_2COX$

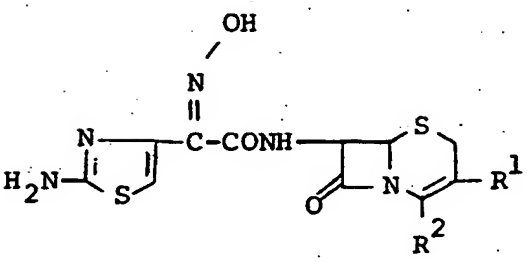
Reaction with 7-amino-3-cephem compounds



Nitrosation



Ring Formation by thiourea



(I)

wherein R^1 and R^2 are each as defined above,
R^a is carboxy-protecting group such as ethyl,
R^b is amino-protecting group such as chloroacetyl,
R^4 is hydroxy-protecting group, and
X and Y are each halogen.

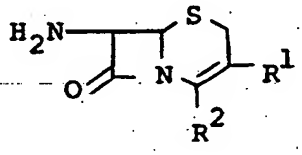
With respect to Method 1, however, two superfluous steps, that is, introduction of the amino-protecting group and elimination of the amino-protecting group, are required and therefore the total yield of the object cephem compound is not so high.

With respect to Method 2, expensive cephem compounds

have to be used in early stage and therefore it costs very high to obtain the final compounds, and further in this method anti isomer on the oxime moiety is also produced and so it requires additional separation step of the anti isomer.

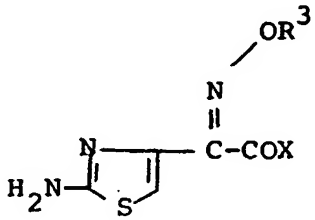
The inventors of the present invention have intensively studied various methods for industrial production of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds, and as a result thereof they have succeeded in separating 2-(2-aminothiazol-4-yl)-2-acyloxyiminoacetyl halide or its acid addition salt in a stable form and completing the new process of the present invention.

The process of the present invention is characterized by reacting 7-amino-3-cephem compounds of the formula :



(II)

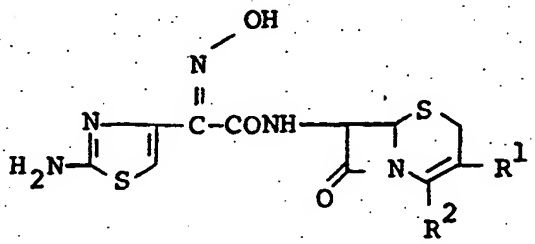
wherein R^1 and R^2 are each as defined above, or its reactive derivative at the amino group or a salt thereof, with 2-(2-aminothiazol-4-yl)-2-acyloxyiminoacetyl halide of the formula :



(III)

wherein R^3 is acyl and X is as defined above,

or a salt thereof, and then by subjecting the resultant compound to elimination reaction of the acyl group on R^3 to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido)-3-cephem compounds of the formula :

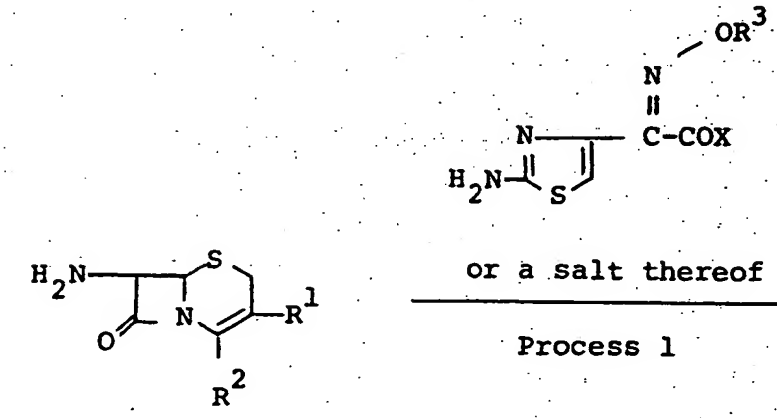


(I)

wherein R^1 and R^2 are each as defined above, or a salt thereof.

Suitable salt of the starting compound (II) and the object compound (I) may be a conventional one used in the cephalosporin and penicillin field and may include a salt with a base or an acid addition salt such as a salt with an inorganic base for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.) etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); and the like, and suitable salt of the starting compound (III) may be the acid addition salt as exemplified above.

The process of the present invention can be illustrated by the following reaction scheme.



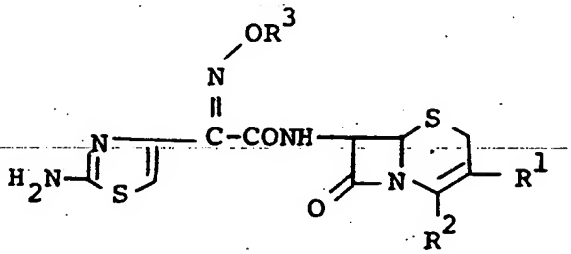
(III)

or a salt thereof

Process 1

(II)

or its reactive derivative at the amino group or a salt thereof

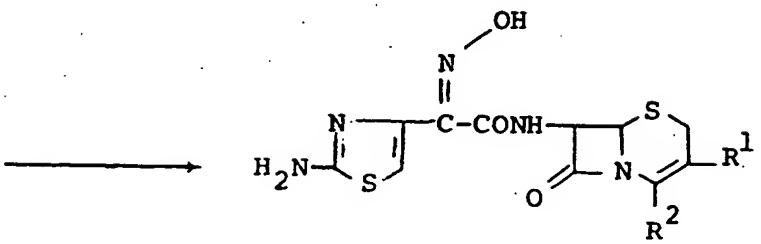


Elimination of the acyl group on R^3

Process 2

(IV)

or a salt thereof

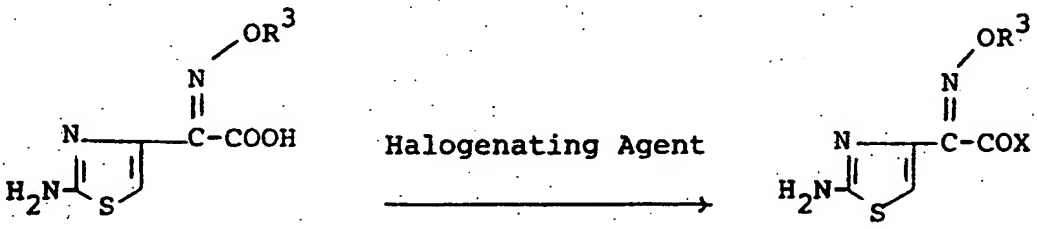


(I)

or a salt thereof

wherein R^1, R^2 and R^3 are each as defined above.

The starting 2-(2-aminothiazol-4-yl)-2-acyloxyimino-acetyl halide (III) includes new compounds, and they can be prepared by the following reaction scheme.



(IIIa)
or a salt thereof

(III)
or a salt thereof

wherein R^3 and X are each as defined above.

The 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacet-amido]-3-cephem compounds (I) obtained by the process of the present invention exhibit high antimicrobial activity, inhibiting the growth of wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents.

In the above description of the present specification, suitable examples and illustrations of the definitions for R^1, R^2 and R^3 are explained in detail as follows.

The term "lower" used in the present specification is intended to mean a group having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "acyl" group may include aliphatic acyl group and acyl group containing an aromatic or hetero-cyclic ring. And, suitable examples of the said acyl may

be lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);
lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.);
lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.);
arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.);
aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl,

(to be continued to the next page)

phthaloyl, indancarbonyl, etc.);
ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.);
ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.
The acyl moiety as stated above may have at least one suitable substituent(s) such as halogen (chlorine, bromine, fluorine and iodine) or the like.

Suitable "protected carboxy" group may include an esterified carboxy group which is conventionally used in penicillin or cephalosporin compounds at their 3rd or 4th position thereof.

Suitable "ester moiety" in "esterified carboxy group" may include lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.), lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.), lower alkoxy-(lower)alkyl ester (e.g. methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxy-ethyl ester, 1-ethoxyethyl ester, etc.), lower alkylthio(lower)alkyl ester (e.g. methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester isopropylthiomethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy-(lower)alkyl ester (e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, isobutyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, 1-acetoxypropyl ester, etc.), lower alkanesulfonyl-(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester, etc.), ar(lower)alkyl ester which may have one

or more substituent(s) such as mono(or di or tri)phenyl-(lower)alkyl ester which may have one or more suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.), aryl ester which may have one or more suitable substituents (e.g. phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, salicyl ester, etc.), heterocyclic ester (e.g. phthalidyl ester, etc.), trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl , triethylsilyl, isopropyldimethylsilyl, tert-butyldimethylsilyl, diisopropylmethylsilyl, etc.), triarylsilyl (e.g. triphenylsilyl, etc.), triar(lower)alkylsilyl (e.g. tribenzylsilyl, etc.), and the like.

Suitable "an organic group" may be a conventional group used in the third position of cephalosporin compounds and may include aliphatic, aromatic and heterocyclic group, for example, lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.);

lower alkenyl (e.g. vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.);

aryl (e.g. phenyl, tolyl, xylyl, cumenyl, naphthyl, etc.);

heterocyclicthiomethyl (e.g. furylthiomethyl, thiazolylthiomethyl, thiadiazolylthiomethyl, tetrazolylthiomethyl, etc.);

heterocyclicmethyl having quaternary nitrogen atom (e.g. 1-lower alkylpyrrolidiniomethyl such as 1-methylpyrrolidiniomethyl, 1-ethylpyrrolidiniomethyl, 1-methyl-2-hydroxymethylpyrrolidiniomethyl, 1-methyl-2-carbamoyloxymethylpyrrolidiniomethyl, etc.).

Suitable "halogen" may include chloride, bromide, iodine, and the like.

The preferred embodiments of the definitions for R^1, R^2 and R^3 are as follows.

R^1 is lower alkenyl, (e.g. vinyl, etc.); or heterocyclic-thiomethyl, preferably 5-membered aromatic heterocyclic group containing one sulfur atom and one to two nitrogen atom(s) (e.g. 1,2,4-thiadiazolyl, etc.);

R^2 is carboxy or esterified carboxy, preferably tri(lower)alkylsilyloxycarbonyl, preferably tri(C_1-C_4)alkyl silyloxycarbonyl (e.g. trimethylsilyloxycarbonyl, etc.); and

R^3 is lower alkanoyl, preferably C_1-C_4 alkanoyl (e.g. acetyl, etc.).

The processes for preparing the object compound (I) in the present invention are explained in detail in the following.

Process 1

The compound (IV) or a salt thereof can be prepared by reacting a compound (II) or its reactive derivative at the amino group or a salt thereof with 2-(2-aminothiazol-4-yl)acyloxyiminoacetyl halide (III) or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide or the like.

Suitable salt of the compound (IV) may be the salt

X

as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction may be carried out in the absence or in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling or at ambient temperature.

The present reaction includes, within its scope, the case that the carboxy-protective group for R^2 is eliminated during the reaction or the post-treating step of the present process.

The compound (III) or its salt used in this reaction has been isolated in a stable form for the first time by the inventors of the present invention, by which the reaction proceeds in high yield and becomes very convenient because no removal step of the side products is needed and the amounts of the reactants can be easily controlled in the best conditions.

Process 2

The compound (I) or a salt thereof can be prepared by subjecting the compound (IV) or a salt thereof to elimination reaction of the acyl group on R^3.

This elimination reaction is preferably carried out in the same reaction medium as Process 1 (one pot) without isolation of the compound (IV).

The present elimination reaction is carried out in accordance with a conventional method such as hydrolysis; reduction; or the like.

The hydrolysis may include a method using an acid or a base and the like. These methods may be selected depending on the kind of the acyl groups to be eliminated.

Suitable acid may include an organic or an inorganic acid, for example, formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrochloric acid and the like. Further, instead of the above acid, Lewis acid such as boron trifluoride etherate and the like can also be used in this reaction. The acid suitable for the reaction can be selected according to the kind of acyl group to be eliminated. When the elimination reaction is conducted by the acid, it can be carried out in the presence or absence of a solvent. Suitable solvent may include an organic solvent such as alcohol (e.g. methanol, etc.).

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like. The hydrolysis using a base is often carried out in water or a hydrophilic

organic solvent or a mixed solvent thereof.

The reduction may include, for example, reduction with an alkali metal borohydride (e.g. sodium borohydride, etc.), catalytic reduction using conventional catalyst and the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The present elimination reaction includes, within its scope, the case that the carboxy-protective group for R^2 is eliminated during the reaction or the post-treating step of the present process.

The process of the present invention is very useful for industrially preparing antimicrobial 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido)-3-cephem compounds (I) in high yield, especially 3-vinyl-3-cephem compound.

The process for the preparation of the starting 2-(2-aminothiazol-4-yl)-2-acyloxyiminoacetyl halide (III) or a salt thereof is explained hereinbelow.

The starting compound (III) or a salt thereof can be prepared by reacting the compound (IIIa) with a halogenating agent.

Suitable salt of the compound (III) may be the salt with a base and that of the compound (IIIa) may be the salt with a base or the acid addition salt as exemplified for the compound (I).

The compound (IIIa) can be prepared by the method described in the Preparations mentioned later or by a conventional method.

Suitable halogenating agent used in this reaction may be a conventional one which is capable of transforming a

carboxylic acid to its acid halide such as phosphorus pentachloride, phosphorus oxychloride, thionyl chloride, phosgene, and the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as methylene chloride, chloroform, and the like. The reaction temperature is not critical, and the reaction is preferably carried out under cooling to at ambient temperature.

The acid addition salt, such as hydrochloride, of the compound (III) can be isolated in a stable crystalline form and is particularly preferable for the reaction of the present invention.

The following preparations and examples are given for the purpose of illustrating the present invention.

Preparation 1

To a suspension of ethyl 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate (syn isomer) (172 g) in ethanol (1.6 ℓ) was added dropwise 1N aqueous sodium hydroxide (840 ml) at 48°C under stirring over a period of 30 minutes. After the addition, the stirring was continued for 1.5 hours at the same temperature. The reaction mixture was cooled to 5°C and after being stirred at 5°C for 1 hour, the precipitates were collected by filtration, washed with ethanol and dried in vacuo over phosphorus pentoxide to give sodium 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate dihydrate (syn isomer) (156.7 g).

mp: 130-131°C (dec.)

IR (Nujol*): 3520, 3300, 1600, 1530 cm^{-1}

*Registered Trademark

NMR (DMSO-d_6, δ) : 6.97 (2H, br s), 7.33 (1H, s)

This compound (20 g) was recrystallized from water (30 ml) to give the pure compound (12.6 g).

mp : 133-134°C (dec.)

Analysis Calcd. for $C_5H_4N_3O_3SNa \cdot 2H_2O$:

C 24.49, H 3.27, N 17.14, S 13.06, Na 9.39, H_2O 14.69

Found : C 24.65, H 3.31, N 17.38, S 13.31, Na 9.67, H_2O 14.75

Preparation 2

To a solution of sodium 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate dihydrate (syn isomer) (20.9g) in water (150ml) was added acetic anhydride (23.5 g) at 23 - 25°C over a period of 50 minutes. During the addition, the reaction mixture was kept to PH 6.0 - 6.3 by addition of 10% aqueous potassium carbonate. After the stirring was continued for 20 minutes, the reaction mixture was acidified to PH 3.0 by addition of 6N hydrochloric acid. The resulting precipitate was collected by filtration, washed with ethanol and diisopropyl ether successively and then dried in vacuo over phosphorus pentoxide to give 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetic acid (syn isomer) containing 1.1 molecule of water (17.6 g).

mp : 138-140°C (dec.)

IR (Nujol) : 3400,3100, 1760, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 7.25 (1H, s)

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Preparation 3

To a solution of phosphorus pentachloride (25.0 g) in methylene chloride (250 ml) was added 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetic acid (syn isomer) (12.5 g) in a portion at -20°C under stirring. The stirring was continued for 75 minutes at -10 ∿ -15°C. To the reaction mixture was added dropwise diisopropyl ether (250 ml) over a period of 15 minutes below 0°C. The resulting precipitate was collected by filtration, washed with diisopropyl ether and then dried over phosphorus pentoxide in vacuo to give crystalline 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetyl chloride hydrochloride (syn isomer) (13.3 g).

mp : 128-130°C (dec.)

IR (Nujol) : 3300, 1800, 1780, 1640, 1590 cm^{-1}

Preparation 4

To a solution of sodium 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate dihydrate (syn isomer) (49.0 g) in N,N-dimethylformamide (240 ml) was added dropwise acetic anhydride (40.8 g) at 25°C over a period of 30 minutes under stirring. The stirring was continued for additional 30 minutes before ethyl acetate (240 ml) was added to the reaction mixture. After being stirred for an hour at 5°C, crystals were collected by filtration to give sodium 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetate N,N-dimethylformamide (syn isomer) (58.84 g).

(to be continued to the next page)

IR (Nujol) : 3300, 3100, 1765, 1660, 1620, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.25 (3H, s), 2.87 (3H, s), 3.02 (3H, s), 7.18 (1H, s), 7.93 (1H, s)

Preparation 5

To a solution of sodium 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetate N,N-dimethylformamide (syn isomer) (58.8 g) in water (1050 ml) was added active charcoal (5.9 g) at room temperature under stirring. After being stirred for 10 minutes, the mixture was filtrated. The filtrate was adjusted to pH 2.5 with 6N hydrochloric acid and then stirred at 5 - 10°C for 3 hours. The precipitates were collected by filtration to give 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetic acid dihydrate (syn isomer) (44.5 g).

IR (Nujol) : 3450, 3100, 1750, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.17 (3H, s), 7.20 (1H, s)

Analysis Calcd. for $C_7H_7N_3O_4S \cdot 2H_2O$:

C 31.70, H 4.15, N 15.85, S 12.08, H_2O 13.58

Found : C 31.86, H 3.82, N 16.06, S 12.26, H_2O 13.39

Example 1

To a solution of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (4.52 g) and bis(trimethylsilyl)acetamide (8 ml) in tetrahydrofuran (50 ml) was added 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetyl chloride hydrochloride (syn isomer) (6.8 g) in small portions at 0°C under stirring. The stirring was continued for 1 hour at 0 - 5°C. The reaction mixture was poured into cold water (250 ml) and then the resulting precipitate was collected by filtration, washed with cold water, dried over phosphorus pentoxide in vacuo to give 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (7.44 g) (Yield : 85.1 %).

IR (Nujol) : 3250, 1770, 1750, 1705, 1650, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 3.60, 3.87 (2H, ABq, J=18Hz), 5.23 (1H, d, J=5Hz), 5.32 (1H, d, J=10Hz), 5.60 (1H, d, J=17Hz), 5.82 (1H, dd, J=8Hz, J=5Hz), 6.92 (1H, dd, J=10Hz, J=17Hz), 7.17 (1H, s), 9.97 (1H, d, J=8Hz)

Example 2

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (1.3 g) and ammonium chloride (481.5 mg) in a mixture of water (21 ml) and methanol (15 ml) was added dropwise 10% aqueous potassium carbonate at room temperature under stirring until the reaction mixture reached to pH 8.0. The stirring was continued for 1.5 hours at the same temperature keeping to pH 8.0 by addition of 10% aqueous potassium carbonate. After the reaction mixture was adjusted to pH 5.0 by addition of 1N hydrochloric acid, the methanol was evaporated in vacuo. The residual aqueous solution was adjusted to pH 2.5 by addition of 1N hydrochloric acid and then stirred at 5 - 10°C for 30 minutes. The resulting precipitate was collected by filtration, washed with cold water and then dried over phosphorus pentoxide in vacuo to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (830 mg) (Yield : 70.0%).

IR (Nujol) : 3300, 1780, 1660, 1605, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.53, 3.80 (2H, ABq, J=18Hz), 5.17 (1H, d, J=5Hz), 5.28 (1H, d, J=10Hz), 5.57 (1H, d, J=17Hz), 5.75 (1H, dd, J=8Hz, J=5Hz), 6.65 (1H, s), 6.90 (1H, dd, J=17Hz, J=10Hz), 7.07 (2H, br s), 9.42 (1H, d, J=8Hz), 11.25 (1H, br s)

Example 3

To a solution of 7-amino-3-(1,2,4-thiadiazol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid (990 mg) and monotrimethylsilylacetamide (3.0 g) in tetrahydrofuran (15 ml) was added 2-(2-aminothiazol-4-yl)-2-acetoxyimino-acetyl chloride hydrochloride (syn isomer) (937.2 mg) in a portion at 5°C under stirring. The stirring was continued for 1 hour at 0 - 5°C. The reaction mixture was poured into a mixture of ethyl acetate (30 ml) and cold water (30 ml). The organic layer was separated, washed with aqueous saturated sodium chloride, dried over magnesium sulfate and then evaporated in vacuo. The residue was triturated with diisopropyl ether to give 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-(1,2,4-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (syn isomer) (1.45 g) (Yield : 89.3%).

IR (Nujol) : 3300, 1770, 1660, 1610, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 3.57, 3.77 (2H, ABq, J=18Hz), 4.30, 4.60 (2H, ABq, J=14Hz), 5.17 (1H, d, J=5Hz), 5.82 (1H, dd, J=8Hz, J=5Hz), 7.04 (1H, s), 7.30 (2H, br s), 8.70 (1H, s), 9.90 (1H, d, J=8Hz)

Example 4

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-(1,2,4-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (syn isomer) (1.08 g) and ammonium chloride (321 mg) in a mixture of water (15 ml) and methanol (10 ml) was added dropwise 10% aqueous potassium carbonate at room temperature under stirring until the reaction mixture reached to pH 8.0. The stirring was continued for 1.5 hours at the same temperature keeping to pH 8.0 by addition of 10% aqueous potassium carbonate. After the reaction mixture was adjusted to pH 6.0 by addition of 1N hydrochloric acid,

the mixture was evaporated in vacuo to remove the methanol. The residual aqueous solution was adjusted to pH 2.5 by addition of 1N hydrochloric acid and then stirred at 5 - 10°C for 30 minutes. The resulting precipitate was collected by filtration, washed with cold water and then dried over phosphorus pentoxide in vacuo to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1,2,4-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (syn isomer) (805 mg) (Yield : 80.6 %).

IR (Nujol) : 3200, 3080, 1760, 1690, 1650, 1605, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 3.73, 3.57 (2H, ABq, J=18Hz), 4.30, 4.60 (2H, ABq, J=14Hz), 5.15 (1H, d, J=5Hz), 5.78 (1H, dd, J=8Hz, J=5Hz), 6.65 (1H, s), 7.07 (1H, br s), 8.70 (1H, s), 9.40 (1H, d, J=5Hz), 11.25 (1H, s)

Example 5

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (1.0 g) in methanol (20 ml) was added conc. hydrochloric acid (0.9 ml). The mixture was stirred at room temperature for 1.5 hours. To the reaction solution was added water (20 ml). The aqueous solution was adjusted to pH 3.0 with aqueous saturated sodium hydrogen carbonate filtered to remove a small amount of insoluble materials and evaporated in vacuo to remove the methanol. To the residue was added aqueous saturated sodium chloride (30 ml) and then stirred at room temperature for 30 minutes. The resulting crystals were collected by filtration and washed with water to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (692 mg) (Yield : 76.5%).

IR (Nujol) : 3300, 1780, 1660, 1605, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.53, 3.80 (2H, ABq, J=18Hz),

5.17 (1H, d, J=5Hz), 5.28 (1H, d, J=10Hz), 5.57 (1H, d, J=17Hz), 5.75 (1H, dd, J=8Hz, J=5Hz), 6.65 (1H, s), 6.90 (1H, dd, J=17Hz, J=10Hz), 7.07 (2H, br s), 9.42 (1H, d, J=8Hz), 11.25 (1H, br s)

Example 6

To a solution of benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate·hydrochloride (2.14 g) and bis(trimethylsilyl)urea (2.04 g) in tetrahydrofuran (25 ml) was added 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetyl chloride·hydrochloride (syn isomer) (1.7 g) at 0 - 5°C under stirring. The stirring was continued at 0 - 5°C for 30 minutes. To the reaction mixture were added ethyl acetate (50 ml) and water (25 ml). The resulting precipitates were collected by filtration to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate·hydrochloride·ethyl acetate (syn isomer) (3.26 g) (Yield : 89.6%).

IR (Nujol) : 1780, 1760, 1705, 1690, 1680, 1630, 1580, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 3.67, 3.87 (2H, ABq, J=18Hz), 5.27 (1H, d, J=5Hz), 5.30 (1H, d, J=10Hz), 5.65 (1H, d, J=17Hz), 5.88 (1H, d, J=8Hz, J=5Hz), 6.75 (1H, dd, J=17Hz, J=10Hz), 6.92 (1H, s), 7.17 (1H, s), 7.33 (10H, s), 9.97 (1H, d, J=8Hz)

Example 7

To a suspension of benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate·hydrochloride (purity : 94.5%) (2.27 g) and ethyl acetate (65 ml) in tetrahydrofuran (25 ml) was added water (25 ml) containing sodium bicarbonate (1.68 g) under stirring at 5°C. The mixture was stirred at 5°C for 5 minutes. To this mixture was added portionwise 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetyl chloride·hydrochloride (syn isomer) (2.13 g) under stirring for 10 minutes. To the residue was added aqueous saturated sodium bicarbonate (2 ml) and then stirred at 5°C for 15 minutes. The precipitate was filtered and the organic layer was separated, added 1N hydrochloric acid (25 ml) at 5°C for 15 minutes under stirring. The resulting precipitate was collected by filtration, washed with ethyl acetate to give benzhydryl 7-[2-(2-amino-thiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate·hydrochloride·ethyl acetate (syn isomer) (3.58 g) (yield : 98.4%).

IR (Nujol) : 1780, 1760, 1705, 1690, 1680, 1630, 1580, 1530 cm^{-1}

Example 8

To a suspension of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate·hydrochloride·ethyl acetate (syn isomer) (300 mg) in methanol (3 ml) was added boron trifluoride etherate (350 mg) at room temperature. The mixture was stirred at the same temperature for an hour. To the mixture was added isopropyl ether and the precipitate was collected by filtration, washed with isopropyl ether and dried to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate·hydrochloride (syn isomer) (220 mg) (yield : 89.4%).

NMR (DMSO-d_6, δ) : 3.61, 3.92 (2H, ABq, J=13Hz), 5.28 (1H, d, J=5Hz), 5.29 (1H, d, J=10Hz), 5.64 (1H, d, J=17Hz), 5.87 (1H, dd, J=5Hz, 8Hz), 6.75 (1H, dd, J=10Hz, 17Hz), 6.87 (1H, s), 6.93 (1H, s), 7.35 (13H, m), 9.70 (1H, d, J=8Hz), 12.30 (1H, broad)

The following compound can be prepared by subjecting the above compound to a conventional method.

7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)

Example 9

To a solution of benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate·hydrochloride (2.27 g) in a mixture of methylene chloride (12.5 ml) and formic acid (230 mg) was added boron trifluoride etherate (1.42 g) at 20°C under stirring. After being stirred at 20~23°C for an hour, the reaction mixture was added dropwise tetrahydrofuran (12.5 ml) and added bis(trimethylsilyl) urea (3.58 g) under stirring for 10 minutes. To the mixture was added 2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetyl chloride·hydrochloride (syn isomer) (1.56 g) at 5°C for an hour under stirring. To the reaction mixture was added aqueous saturated sodium chloride (25 ml) and then stirred at 5°C for 10 minutes. The resulting precipitate was collected by filtration, washed with aqueous saturated sodium chloride, dried to give 7-[2-(2-aminothiazol-4-yl)-2-acetoxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid·hydrochloride (syn isomer) (3.53 g) (yield: 91.9%).

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 3.59, 3.90 (2H, ABq, J=13Hz), 5.24 (1H, d, J=5Hz), 5.32 (1H, d, J=11Hz), 5.59 (1H, d, J=17Hz),

5.80 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, dd, J=11Hz, 17Hz), 7.14 (1H, s), 9.94 (1H, d, J=8Hz)

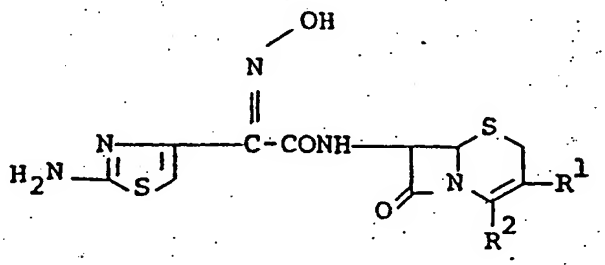
Example 10

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid·hydrochloride (syn isomer) (5.30 g) in methanol (10 ml) was added dropwise a mixture of conc. sulfuric acid (980 mg) and methanol (5 ml). The mixture was stirred at 23~24°C for 30 minutes and then cooled to 5°C. The reaction mixture was poured into cold sodium bicarbonate (2.52 g) in water (50 ml) and ethyl acetate (30 ml). The aqueous solution was adjusted to pH 5.0 with aqueous saturated sodium bicarbonte (3.5 ml), filtered to remove a small amount of insoluble materials. The aqueous layer was evaporated in vacuo to remove methanol and ethyl acetate. The resulting precipitates were collected by filtration and washed with ice-water to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (3.40 g) (yield : 93.1 %).

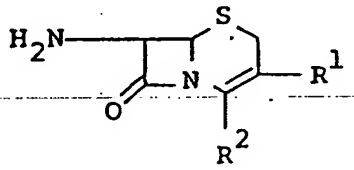
IR (Nujol) : 3300, 1780, 1660, 1605, 1540 cm^{-1}

The embodiments of the invention in which an exclusive property or privilege is claimed, are defined as follows:

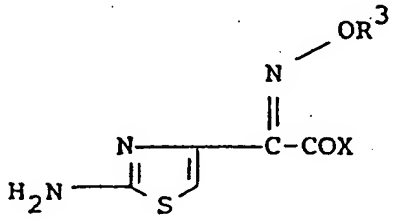
1. A process for the preparation of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds of the formula :



wherein R^1 is lower alkenyl or thiadiazolyl-thiomethyl, and R^2 is carboxy or protected carboxy,
or a salt thereof, which is characterized by reacting 7-amino-3-cephem compounds of the formula :



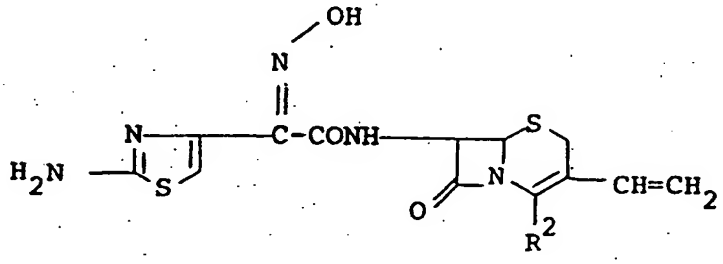
wherein R^1 and R^2 are each as defined above,
or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :



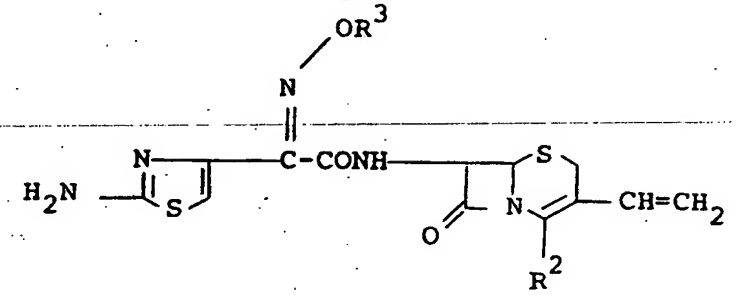
wherein R^3 is acetyl and X is halogen,
or a salt thereof,

and then by subjecting the resultant compound to elimination reaction of the acetyl group on R^3.

2. A process for the preparation of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem compounds of the formula :

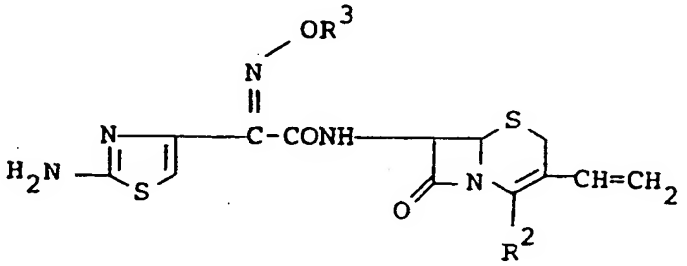


wherein R^2 is carboxy or protected carboxy, or a salt thereof, which is characterized by subjecting 3-cephem compounds of the formula :



wherein R^2 is as defined above and R^3 is acetyl, or a salt thereof to elimination reaction of the acetyl group on R^3.

3. A compound of the formula :



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wherein R^2 is carboxy or protected carboxy, and

R^3 is acetyl,

or a salt thereof.